Epidemiol. Infect. (2017), **145**, 2886–2889. © Cambridge University Press 2017
doi:10.1017/S0950268817002047

Using data linkage to improve surveillance methods for acute hepatitis E infections in England and Wales 2010–2016

C. OESER[1,2]*, B. SAID[1], F. WARBURTON[3], S. IJAZ[4], R. TEDDER[4] AND D. MORGAN[1]

[1] *Emerging Infections and Zoonoses, National Infection Service, Public Health England, London, UK*
[2] *NIHR Health Protection Research Unit in Emerging and Zoonotic Infections, Liverpool, UK*
[3] *Statistics and Modelling Economics Department National Infection Service, Public Health England, London, UK*
[4] *Virus Reference Department, National Infection Service, Public Health England, London, UK*

Received 5 May 2017; Final revision 26 July 2017; Accepted 16 August 2017; first published online 26 September 2017

SUMMARY

Indigenous, foodborne transmission of hepatitis E has been increasing across industrialised countries. Public Health England has conducted enhanced surveillance in England and Wales since 2003.This report gives an account of acute infections from 2010 to 2016 and describes modification made to the methods of surveillance to account for changes in reporting behaviours and improve ascertainment.

Key words: Emerging infections, food-borne zoonoses, infectious disease epidemiology, virus infection.

INTRODUCTION

Hepatitis E virus (HEV) is found worldwide. HEV usually causes a mild and often self-limiting infection of the liver. It is an RNA virus with four main genotypes; G1–G4. G1 and G2 have so far only been found in humans, and are known for causing acute disease in travellers returning from hyper-endemic countries where it occurs sporadically or in large outbreaks (South Asia, Middle East, Africa and Mexico). In contrast, cases in industrialised countries are mainly sporadic and caused by G3 (Europe, North America and Japan) and G4 viruses (South East Asia). Both G3 and G4 viruses are enzootic and have been found in a number of animal species including pigs, wild boar, deer and rabbits. There is evidence that infection is acquired through the consumption of undercooked meat of these animals [1–3].

Over the last decade, cases of acute, non-travel associated HEV G3 infection have been rising across Europe [4] and indigenous foodborne transmission of HEV G3 has been increasingly recognized as an emerging problem in industrialized countries. In the UK, 93% of pigs entering the food chain at the time of slaughter were found to be seropositive for HEV and in 21% HEV RNA was detected, indicating potential for infectiousness [5]. Another study demonstrated the presence of HEV RNA in pork products sampled from a limited number of merchandise at the point of sale from UK retailers [6].

HEV can also be acquired from blood products. In a recent study, one in 3000 blood donations in England tested positive for HEV RNA with a transmission rate of 42% (18 out of 43 patients that were followed up) [7]. Similar prevalence of HEV infection in blood donors has been reported from other countries. Transfusion transmitted infection rarely causes

* Author for correspondence: C. Oeser, Emerging Infections and Zoonoses, National Infection Service, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK.
(Email: Clarissa.oeser@phe.gov.uk)

acute morbidity, but can result in persistent infection in immunocompromised patients such as solid organ transplant recipients, patients with haematological disorders and HIV-infection [8].

The predominant HEV genotype in England and Wales is G3, which divides phylogenetically into two main groups. Prior to 2010, HEV G3 group 1 (otherwise known as G3 efg) was the only known G3 phylotype circulating in England and Wales. However, the substantial increase in indigenous HEV cases in recent years has been associated with the emergence of a novel phylotype; HEV G3 group 2 (also known as G3 abcdhij) [9].

Public Health England (PHE) has conducted enhanced surveillance for acute hepatitis E infection in England and Wales since 2003 to monitor trends and describe the characteristics of cases and potential risk factors. This report outlines the recent changes to the methods of surveillance of HEV to improve case ascertainment, and provide a better estimate of numbers of laboratory diagnosed cases.

METHODS

Two national surveillance systems are used to estimate the burden of acute infection with HEV in England and Wales. Both are based on reporting of HEV test results of patients presenting with signs and symptoms suspicious of acute hepatitis.

The first system, established in 2003, is the enhanced surveillance system based on reference laboratory data. There are two PHE reference laboratories where HEV antibody and HEV RNA testing is provided; the Virus Reference Department (VRD) and the Midlands Public Health Laboratory. VRD employs the Wantai assays (Fortress Diagnostics, Northern Ireland) for HEV IgM and IgG detection. The Midlands Public Health Laboratory uses the recomWell assays (Mikrogen; Neuried, Germany). For detection and sequencing of HEV RNA, nucleic acid is extracted using either the Universal BioRobot platform (Qiagen, Hilden, Germany) or the Magna Pure 96 platform (Roche Diagnostics Ltd, UK) and subjected to reverse transcription and polymerase chain reaction (PCR) amplification, initially using a taqman assay and since late 2012 a modified Taqman assay. Sequencing, genotypic and phylogenetic analysis across part of the ORF2 is undertaken on all HEV RNA positive samples with a viral load >5000 IU/ml as described previously [9].

Acute HEV infection is confirmed in a patient with acute hepatitis if samples tested positive for either HEV RNA or for HEV IgM and IgG (see https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/396909/PH_Operational_Guidelines_for_HepE_051214_Standard_template_CT.pdf).

For surveillance purposes, the patient's name, date of birth, post code and travel history are collected from laboratory request forms. Duplicates are identified by their name and date of birth and removed.

The second system is the PHE's Second Generation Surveillance System (SGSS). HEV is a causative organism notifiable to PHE under the Health Protection (Notification) Regulations 2010. Diagnostic laboratories have a duty to notify the PHE electronically through the SGSS when they identify evidence of HEV infection. Although there may be variation in testing methods across local laboratories, this is minimised by all hospital microbiology laboratories in England being accredited, and a requirement of accreditation is participation in the assessment scheme run by the UK National External Quality Assessment Service (NEQAS). Case definitions for acute HEV infection may also differ across local laboratories, for example, a patient could be considered a case on the basis of a positive IgM result alone.

The patient's name, date of birth and post code is also available in SGSS and cases reports through this system are de-duplicated as above.

In addition, PHE's local health protection teams follow up new cases of HEV and request a surveillance questionnaire is completed to record the patient's clinical presentation and exposures representing potential risk factors, including details on travel and dietary behaviours.

To improve ascertainment, all acute cases of HEV infection in England and Wales reported through the PHE reference laboratories and SGSS from 1 January 2010 to 31 December 2016 were collated and concordance of cases was checked by comparing name and date of birth. SGSS data are now routinely linked with data from the reference laboratories and reported quarterly by PHE. (See https://www.gov.uk/government/collections/health-protection-report-latest-infection-reports#zoonoses).

Logistic regression was used to adjust for the increase in number of tests performed (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

RESULTS

From 2010 to 2016, 4851 cases of acute HEV infection were identified by the two reference laboratories. A year on year increase in numbers was reported during

https://doi.org/10.1017/S0950268817002047 Published online by Cambridge University Press

Table 1. *New cases of HEV infection reported by the reference laboratories and SGSS 2010-2016*

Year	Reference laboratories	SGSS	Total	Incidence/ 100 000
2010	276	171	368	0·6
2011	464	265	536	0·9
2012	605	359	714	1·2
2013	731	389	845	1·4
2014	925	596	1062	1·7
2015	959	748	1212	1·9
2016	891	759	1243	1·9

this time apart from 2016 when numbers decreased. An increase in numbers of acute HEV infections by year could also be observed in reports from SGSS. Over the same period (2010–2016) 3287 cases were reported. In comparison with reports from the reference laboratories, the increase was particularly evident between 2014 and 2016. Table 1 shows the number of cases reported each year through the two surveillance systems and the total combined number of cases from both surveillance systems after de-duplication both within and between the datasets. The number of cases more than tripled from 2010 to 2016 (368–1243 cases) and the incidence rate rose from 0·6/100 000 in 2010 to 1·9/100 000 in 2016.

To investigate the likelihood of surveillance bias affecting this analysis, all samples that underwent testing for HEV at the PHE reference laboratories from 2010 to 2016 were collated. The number of samples tested for HEV almost quadrupled from 3453 samples in 2010 to 13 787 samples in 2016. Analysis using logistic regression showed that, after adjusting for the increasing number of tests performed, there was a significant increase in HEV cases reported in the period from 2011 to 2013 compared with 2010. Thereafter, the increase in numbers was not significant.

A genotype was identified in 1743 cases. The majority were reported as G3 ($n = 1480$, 85%) and G1 was detected in 261 cases (15%).

DISCUSSION

HEV infection was generally thought to be a travel-related infection acquired overseas in hyper endemic countries. However, locally acquired HEV infection has been increasingly detected across Europe. Enhanced surveillance in England and Wales has shown a year on year increase in HEV infections in England and Wales from 2010 to 2016. The continuing increase in cases can be attributed to locally acquired infections with HEV G3.This genotype is of increased significance as it can become chronic in immunocompromised individuals, which is associated with poor outcomes. A new group within G3, G3 group 2 emerged in 2006 and has been responsible for the continued increase in numbers.

Until fairly recently the majority of testing for HEV was done in the reference laboratories and therefore the enhanced surveillance system alone was an accurate reflection of the numbers of cases with acute hepatitis E infection being diagnosed. However, in more recent years, notifications to the SGSS have been used to supplement reference laboratory surveillance by providing reports from laboratories with local HEV testing capacity. Linkage of reports from both surveillance systems will monitor trends in HEV infections more comprehensively in England and Wales.

There are limitations of this surveillance system. Unlike cases confirmed by the reference laboratories, cases reported through SGSS may not fulfil the case definition for acute hepatitis E outlined by PHE operational guidelines as described above but adhere to different laboratory criteria e.g. IgM positivity only, as proposed by WHO (http://www.who.int/hepatitis/publications/hep-surveillance-guide-pub/en/). Reporting of notifiable organisms is a legal requirement under Health Protection regulations and implementation of electronic reporting has simplified this process. However, as it is unclear how complete reporting is even for acutely life threatening conditions such as meningococcal disease, underreporting of usually mild conditions such as HEV infections is likely. Therefore, data derived from SGSS needs to be interpreted with caution.

Surveillance of HEV infection is increasingly dependent on SGSS data as laboratories are developing capacity to perform their own testing. An understanding of the changing diagnostic capacity across England and Wales has led to the incorporation of this additional surveillance system to the established reference laboratory surveillance scheme. Linkage of these systems will enable continuing monitoring of trends, providing the best estimate of laboratory diagnosed acute cases. Ongoing surveillance is required to identify the source of the increase in HEV infections and provide evidence for appropriate policy development.

ACKNOWLEDGEMENTS

The research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Emerging and Zoonotic Infections

at University of Liverpool in partnership with Public Health England (PHE), in collaboration with Liverpool School of Tropical Medicine. Clarissa Oeser is based at PHE. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

REFERENCES

1. **Li TC, *et al.*** Hepatitis E virus transmission from wild boar meat. *Emerging Infectious Diseases* 2005; **11**(12): 1958–1960.
2. **Tei S, *et al.*** Zoonotic transmission of hepatitis E virus from deer to human beings. *Lancet* 2003; **362**(9381): 371–373.
3. **Said B, *et al.*** Hepatitis E virus in England and Wales: indigenous infection is associated with the consumption of processed pork products. *Epidemiology & Infection* 2014; **142**(7): 1467–1475.
4. **Adlhoch C, *et al.*** Hepatitis E virus: assessment of the epidemiological situation in humans in Europe, 2014/15. *Journal of Clinical Virology* 2016; **82**: 9–16.
5. **Grierson S, *et al.*** Prevalence of hepatitis E virus infection in pigs at the time of slaughter, United Kingdom, 2013. *Emerging Infectious Diseases* 2015; **21**(8): 1396–1401.
6. **Berto A, *et al.*** Hepatitis E virus in pork food chain, United Kingdom, 2009–2010. *Emerging Infectious Diseases* 2012; **18**(8): 1358–1360.
7. **Hewitt PE, *et al.*** Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. *Lancet* 2014; **384**(9956): 1766–1773.
8. **Kamar N, *et al.*** Hepatitis E virus: chronic infection, extra-hepatic manifestations, and treatment. *Clinics and Research in Hepatology and Gastroenterology* 2015; **39** (1): 20–27.
9. **Ijaz S, *et al.*** Indigenous hepatitis E in England and Wales from 2003 to 2012: evidence of an emerging novel phylotype of viruses. *Journal of Infectious Diseases* 2014; **209** (8): 1212–1218.